How Is the NaCl Signal Transmitted in NaCl-Induced Hypertension?

Jong Y. Lee, Louis Tobian, Susan Hanlon, Rochelle Hamer, Mary Ann Johnson, and Junichi Iwai

Is the NaCl signal perceived as a small increase in the concentration of NaCl in extracellular fluid? We used 8 g NaCl/100 g soluble nutrients and fed only a hypertonic (1.4% NaCl) or a hypotonic (0.45% NaCl) drink to Dahl salt-sensitive (DS) rats. After 12 weeks, 11 rats receiving the hypertonic drink had a mean blood pressure of 195 mm Hg versus 195 mm Hg in 12 rats receiving the hypotonic drink. Thus, the high-NaCl signal seems unrelated to a higher NaCl concentration in extracellular fluid, thereby suggesting volume signals. Most volume controls are near the third brain ventricle (3V). As a working hypothesis, high dietary NaCl may swell the tissues surrounding 3V, which is slitlike. Such swelling would partially close the upper part of the slit and cause ependymal cells and nerve fibers on opposite walls to touch, possibly leading to hypertension in susceptible humans or rats. To test this, we stereotaxically blocked the aqueduct with inert silicone to produce hydrocephalus of 3V in DS rats and thus prevent ependymal cells and nerve fibers from touching. After blocking or sham-blocking the aqueduct, either a 6% NaCl diet or a 0.23% NaCl diet was started. Intra-arterial blood pressure was taken after 6 weeks. A group of 28 sham-blocked rats and a group of 29 blocked rats, all fed a 0.23% low NaCl diet, had equal blood pressures averaging 130 mm Hg. Forty-six sham-blocked rats fed the 6% NaCl diet averaged 175±3.0 mm Hg blood pressure, whereas 52 blocked rats fed the 6% NaCl diet averaged 149±3.2 mm Hg blood pressure. Thus, with 6% NaCl, blood pressure rose 45 mm Hg in sham-blocked rats and only 19 mm Hg in blocked rats, a 58% reduction (p<0.001). After 12 weeks on the 6% NaCl diet, 43% of the sham-blocked rats had equal blood pressures averaging 130 mm Hg. Forty-six sham-blocked rats fed the 6% NaCl diet averaged 175±3.0 mm Hg blood pressure, whereas 52 blocked rats fed the 6% NaCl diet averaged 149±3.2 mm Hg blood pressure. Thus, with 6% NaCl, blood pressure rose 45 mm Hg in sham-blocked rats and only 19 mm Hg in blocked rats, a 58% reduction (p<0.001). After 12 weeks on the 6% NaCl diet, 43% of the sham-blocked rats had equal blood pressures averaging 130 mm Hg. Forty-six sham-blocked rats fed the 6% NaCl diet averaged 175±3.0 mm Hg blood pressure, whereas 52 blocked rats fed the 6% NaCl diet averaged 149±3.2 mm Hg blood pressure. Thus, with 6% NaCl, blood pressure rose 45 mm Hg in sham-blocked rats and only 19 mm Hg in blocked rats, a 58% reduction (p<0.001). Twenty-seven other DS rats fed a 6% NaCl diet for 6 weeks underwent thermal lesions of periaqueductal fibers. Their blood pressures were 8 mm Hg higher than 17 rats with sham lesions (p=NS). Thus, the aqueductal block lowered blood pressure apparently not through local injury. The key finding in this study is that an aqueduct block sufficient to produce hydrocephalus will markedly lower blood pressure and mortality rate in NaCl-fed DS rats. The mechanism involved is uncertain and may or may not be explained by our working hypothesis. (Hypertension 1989;13:668-675)

How is the NaCl signal transmitted? When the combination of a high NaCl diet plus a kidney with sluggish sodium excretion induces hypertension in a susceptible human or rat, it is still a mystery as to how the NaCl signal is perceived. In certain people, this NaCl signal may not be perceived at all. We see signs of this in individuals who gradually develop renal failure with no hypertension whatsoever and in whom a large expansion of extracellular fluid (ECF) volume for 4 weeks under dialysis conditions leads to no rise of blood pressure (BP). This lack of reception of the NaCl signal may be present in as many as 20% of people. One possible NaCl receptor is the juxtaglomerular cells in the walls of the renal afferent arterioles. An increased ECF volume as well as an increased concentration of NaCl in plasma diminish renin secretion. It is also possible that the signal for excess NaCl could be perceived in the central nervous system. Various lesions in the central nervous system of the Dahl salt-sensitive (DS) rat can greatly attenuate NaCl-induced hypertension. 6-Hydroxydopamine injected into the lateral brain ventricle destroys many catecholamine-containing neurons and reduces NaCl hypertension by 50%.
Bilateral lesions of the paraventricular nuclei will also reduce NaCl hypertension by 50%. A thermal lesion at the anterior end of the third brain ventricle (AV3V area) will reduce NaCl hypertension by 60%. Moreover, a bilateral lesion of the suprachiasmatic nuclei, which are at the bottom of the 3V, will actually increase NaCl hypertension by 15 mm Hg and heart weight/body weight ratios by 15%. Thus, it is essential to have certain central nervous systems intact to produce the full expression of NaCl-induced hypertension. This could indicate the possibility that the NaCl signal is somehow received in the brain.

If such is the case, it would be helpful to know just how the NaCl signal might be received. It is well known that hypertonic NaCl introduced into the lateral brain ventricle will induce a pressor response, and such pressor responses are greatly exaggerated in the prehypertensive DS rat. The NaCl signal is likely to be perceived either as a rise in NaCl concentration or as a localized increase of ECF volume. Both possibilities are considered in these studies. When an excessive amount of NaCl is incorporated in food, eating would transiently increase the NaCl concentration of the ECF, and the signal could be perceived in this way. This hypothesis was investigated in Experiment 1. If a rise in NaCl concentration were not the signal, the most likely alternate signal would be a rise in ECF volume in some specialized receptor area. It is a common experience that a week at an international scientific conference with all the attendant high NaCl food induces some puffiness of feet and hands with difficulty in removing wedding rings. Many control systems involving body water are located in nuclei surrounding the 3V, which is the vertical slitlike structure shown in Figure 1. It is conceivable that a high NaCl diet could induce some puffiness (excessive ECF volume) in the local tissues on either side of the slit that constitutes the 3V (Figure 2). This localized ECF swelling of tissue on either side of the slit could cause the ependymal cells and the unmyelinated nerve fibers that reside in the walls of the slit to touch one another. Such touching might result in a neurogenic or neurohumoral signal, which would indicate an increased ECF volume (see Figure 2). We partially tested this working hypothesis in Experiment 2 by blocking the aqueduct of Sylvius stereotaxically with an inert silicone material in various DS rats.

Materials and Methods

Experiment 1

Two liquid diets with a high NaCl content were prepared and fed to DS rats for 12 weeks starting at

### TABLE 1. Composition of High NaCl Diets in Experiment 1

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutramigen (a complete food-vitamin-mineral formula containing predigested protein)</td>
<td>Mead Johnson, Nutritional Division</td>
<td>9.6 g</td>
</tr>
<tr>
<td>Nutrament (a high-protein chocolate drink)</td>
<td>Drackett Products, Armour Pharmaceutical Company</td>
<td>20 ml</td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>34 µl, containing 1.7 IU</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td></td>
<td>0.136 g</td>
</tr>
<tr>
<td>Sodium caseinate</td>
<td></td>
<td>0.64 g</td>
</tr>
</tbody>
</table>

1.2 g NaCl was then added to these ingredients for one batch of food. With this formulation, 8 g NaCl is combined with 100 g nutrient solids.
FIGURE 3. Histological sections from three Dahl salt-sensitive rat brains showing blockage of the aqueduct of Sylvius (darker areas). The outer parts of the brains were removed to accommodate multiple serial sections of the areas surrounding the aqueduct and the ventricles on the same slide. The section on the right shows some portion of blocking material missing, which occurred during processing or during microtome sectioning of the tissues. (Original magnification, ×7.5)

6 weeks of age with no other food or water offered. These liquid diets contained 8 g NaCl/100 g soluble nutrients. These components were dissolved either in a minimal amount of water to produce a hypertonic liquid diet (1.4% NaCl) or in a much greater volume of water to produce a hypotonic liquid diet (0.45% NaCl). The soluble nutrients for one batch of food consisted of the ingredients shown in Table 1.

This batch of ingredients was dissolved in either 72 ml H2O for the hypertonic liquid diet (1.4% NaCl) or in 300 ml H2O for the hypotonic liquid diet (0.45% NaCl). Eleven DS rats consumed the hypertonic 1.4% NaCl diet, and 12 other DS rats consumed the hypotonic 0.45% NaCl diet. After 12 weeks on these diets, mean BP was measured by direct femoral artery cannulation under light ether anesthesia. Lewis Dahl (personal communication) and Pfeffer et al.11 have reported that this method yields very accurate readings.

Experiment 2
Under pentobarbital anesthesia, the aqueduct of Sylvius was blocked stereotaxically with a local injection of silicone gel combined with epoxy adhesives (Figure 3). The block was confined strictly to the aqueduct, with the 3V and 4V regions remaining intact. All rats with the aqueduct block developed a hydrocephalic enlargement of the lateral ventricles (Figure 4). Sham lesions were made by placing a hole in the usual location on the skull surface, but no cannula entered the brain to ensure that there was no brain lesion from the cannula itself. Either a 6% or a 0.23% NaCl diet was started on the day of surgery. The rats in both diet groups were further subdivided into those with the aqueduct block and those with the sham aqueduct block. At 6 weeks after surgery, the intra-arterial mean BP was obtained by cannulation of the femoral artery under Brevital (50 mg/kg) anesthesia (Eli Lilly and Company, Indianapolis, Indiana). At 6 weeks, a small sample of blood was obtained after the BP reading, followed by replacement with an equal volume of saline solution.

In another series of DS rats maintained on the 6% NaCl diet, a discrete thermal lesion was placed stereotaxically in the same precise location of the aqueduct as that used for the silicone blocking agent with a Radionics RFG-4A Lesion Generator (Radionics Inc., Burlington, Massachusetts). The thermal lesions were made with an electrode tip temperature of 75°C for 1 minute at a current of approximately 7 mA. This was sufficient to cause enough necrosis to produce a discrete hole that would be apparent in the brain section (Figure 5). The lesions, either thermal or silicone block, were

![Diagram showing sham and verified aqueduct block comparison](https://example.com/diagram.png)

**Average width**

**sham aqueduct block (0.86mm)**

**verified aqueduct block (2.79mm)**

FIGURE 4. Photographs of three Dahl salt-sensitive rat brains with verified aqueductal block on the right show a clearly obvious hydrocephalus of the lateral ventricles, but the two sham-blocked brains on the left show no such hydrocephalus. (Original magnification, ×6.5)
verified with hematoxylin-and-eosin-stained brain tissue slides. The whole body of each rat was thoroughly examined for pathological changes. Under pentobarbital anesthesia, the blood was washed out with 100 mM phosphate buffer, and the brain from each rat was fixed by perfusion with 5% neutral formalin through the carotid artery for 15 minutes under a perfusion pressure that equaled each rat’s own mean BP. Thereafter, the brain was immersed in 10% neutral formalin to complete the fixation. Figure 3 shows examples of the silicone block of the aqueduct. Figure 5 shows the subsequent effects of the thermal lesions.

Statistical Methods

Results were analyzed with the two-tailed unpaired Student’s t test. Data are expressed as mean±SEM. A p value of less than 0.05 was considered significant.

Results

Experiment 1

Eleven DS rats consumed the hypertonic 1.4% NaCl diet, and 12 other DS rats consumed the hypotonic 0.45% NaCl diet. Apparently, the rats drank the liquid diet to satisfy their need for calories because those drinking the hypotonic feeding solution consumed a volume about three times greater than that of those drinking the hypertonic solution. After 12 weeks, the body weights were quite similar for the two groups, averaging 458.4±9 g for the hypertonic drink group versus 449.8±7 g for the hypotonic drink group (p=NS). Because the hypotonic group weighed slightly less, they may have ingested slightly less food and slightly less NaCl. However, at the end of 12 weeks on both diets, the intra-arterial mean BP was 195 mm Hg for the hypertonic as well as the hypotonic group. Because just as much of a BP increase occurred when slightly less total NaCl was introduced in a hypotonic fashion, it is quite unlikely that a high NaCl concentration is the signal that produces a rise in BP. If a rise in NaCl concentration is not the signal, the most likely alternate signal would be a rise in ECF volume in some specialized receptor area.

Experiment 2

The block of the aqueduct produced considerable hydrocephalus of the lateral brain ventricles. In Figure 4, stained sections of the three brains on the right show hydrocephalus of the lateral ventricles after block of the aqueduct. The stained sections of the two brains on the left had a sham block that produced no hydrocephalus. In all the rats fed the 6% NaCl diet, the mean width of a lateral ventricle...
FIGURE 6. Bar graph of intra-arterial mean blood pressure (mm Hg) in rats with a sham or verified block of the aqueduct after 6 weeks on either a 0.23% or a 6% NaCl diet.

was 0.86±0.08 mm in the sham-blocked group versus 2.79±0.13 mm in the group with a block of the aqueduct (p<0.001). This amounts to a more than threefold increase. With this much enlargement of the lateral ventricles after the aqueduct block, it would be highly likely to also find some enlargement of the 3V. This enlargement of the 3V was indeed apparent on histological examination. The widths of the 3Vs in the sham-block groups averaged 54±11 μm, while the widths of the 3Vs in the rats with the aqueduct block averaged 207±19 μm. This was almost a fourfold increase in the rats with the aqueduct block (p<0.001), indicating a hydrocephalic enlargement of the 3V.

Twenty-nine DS rats on a 0.23% low NaCl diet had a verified block of the aqueduct, while 28 other DS rats on the same low NaCl diet had a sham aqueduct block. After 6 weeks on these diets, both groups had an intra-arterial mean BP of 130 mm Hg (Figure 6). Thus, the block of the aqueduct had no influence on the BP of DS rats as long as they were on a very low NaCl diet.

Forty-six other DS rats underwent a sham aqueduct block and then began consuming a 6% high NaCl diet. After 6 weeks on the diet, the intra-arterial mean BP of these rats averaged 175±3.0 mm Hg, indicating a 45-mm Hg rise in blood pressure due to the high NaCl diet (Figure 6). In contrast to this, 52 other DS rats underwent a subsequently verified true aqueduct block and then began consuming the 6% high NaCl diet. After 6 weeks on the diet, the intra-arterial mean BP of this group averaged 149±3.2 mm Hg, indicating a 19-mm Hg increase in BP due to the high NaCl diet. Thus, the true aqueduct block abolished 58% of the NaCl-induced rise in BP (p<0.001) (Figure 6). These results appear to support the hypothesis that the touching of ependymal cells and nerve fibers lining the 3V could produce the signal that ultimately raises the BP.

After 12 weeks on the 6% high NaCl diet, the mortality rate for the 49 DS rats with the sham aqueduct block was 43%, whereas the mortality rate for the 52 DS rats with the true aqueduct block was only 8% (Table 2). Thus, the block of the aqueduct resulted in an 82% reduction in mortality rate (p<0.001). There were no deaths among either group of DS rats on the 0.23% low NaCl diet. Cumulative survival curves (Figure 7) indicate the striking increase in survival among the rats with the verified aqueduct block. At the 10th week after surgery, one of 52 of the high NaCl-fed rats with the true aqueduct block had died, whereas 33% of those with the sham aqueduct block had already perished (Table 2).

When the aqueduct is blocked with silicone, it is quite possible that some of the periaqueductal fibers

<table>
<thead>
<tr>
<th>Postsurgery (week)</th>
<th>True lesion</th>
<th>Sham lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats alive</td>
<td>% Dead</td>
<td>No. of rats alive</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>0.00</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
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</tr>
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<td>13.46</td>
</tr>
<tr>
<td>14</td>
<td>43</td>
<td>17.31</td>
</tr>
</tbody>
</table>

NS, not significant.
of passage and nuclei might be destroyed by the pressure of the silicone, thereby reducing BP. To examine this possibility, we made discrete thermal lesions stereotaxically in the periaqueductal structures of other rats just before they began consuming the 6% NaCl diet for 6 weeks. Another group of rats on the same diet had sham lesions. After 6 weeks, the 27 DS rats with the true thermal lesions had an intra-arterial mean BP of 174±4.8 mm Hg, while the 17 rats with the sham thermal lesions averaged 166±5.6 mm Hg. The BP of the rats with thermal lesions was actually higher, but the p value was only 0.16. The thermal lesions caused no hydrocephalus. Mortality rates in both of these groups were similar to the sham-blocked control group shown in Table 2. Thus, a thermal lesion of periaqueductal fibers of passage certainly did not reduce the NaCl-induced hypertension in the DS rats. This strengthens the notion that it is specifically the hydrocephalus that reduces the hypertension and mortality in these NaCl-fed rats. Figure 5 shows examples of the thermal lesions in the aqueduct area. The radio frequency electrode produces enough cell necrosis to cause a discrete hole in the tissue sections.

Discussion

Although the evidence is strong that NaCl is a causal factor in some hypertensions, the precise mechanisms of NaCl hypertension have not been elucidated.2,12-16 The AV3V region plays a critical role in controlling central angiotensin pressor responses.17,18 Lesions made in the central nervous system partially reverse NaCl-induced hypertension.4-6,17-20

Body water,8 thirst,9 and NaCl appetite control systems21 are known to be located in the region of the 3V, which is a slitlike structure. High NaCl diets could increase ECF volume in the tissues surrounding the 3V. This localized swelling of tissues could cause the walls of the slit to touch one another, thereby releasing a neurogenic or neurohumoral signal (Figure 2). There are unmyelinated nerve fibers in the walls of the slit,10 which could be stimulated whenever they touch the opposite wall of the slit. The ependymal cells have small hairlike processes on the cell surface10 that could also touch the opposite wall and then release a neurogenic signal. The tanycytes are especially long ependymal cells that reach into the hypothalamus.10 If they were to touch the opposite wall, they could release neurohumoral substances into the hypothalamus. The reductions in BP in this study are similar to those previously observed with AV3V, paraventricular, or 6-hydroxydopamine lesions in other studies on NaCl hypertension.4-6 However, in this study, we kept the 3V region intact to test this specific hypothesis. After surgery, the rats recovered quickly within hours and showed no behavioral changes in postoperative food and water intake, as has been noted in other brain lesion studies.6,17,18 As shown in Table 2, the NaCl-induced mortality rate was decreased significantly in the group with the verified aqueductal block as early as 7 weeks after surgery. We also observed mesenteric vascular lesions in many rats of the high NaCl sham group, but these lesions were rare in the blocked high NaCl rats. Severe cerebral hemorrhage was often seen in the high NaCl sham group while this phenomenon was not seen in the high NaCl blocked group. Unlike human infant hydrocephalus, the hydrocephalic brains produced in this experiment did not increase the total brain size, measured as brain width inside the skull at the cross-sectional area of the optic chiasm. The mean brain width of rats in the sham- and true-lesioned groups on either 0.23% or 6% NaCl diets were 17.1±0.17, 16.2±0.20, and 15.3±0.63 mm, respectively. These widths were not significantly different between the sham- and true-blocked groups. However, the mean width of both high NaCl-fed sham and blocked rats was slightly smaller than the widths in the 0.23% NaCl groups (p<0.005). We also measured plasma concentrations of Na+ at 6 weeks after surgery. They did not show any statistical difference between groups, regardless of NaCl or lesion status.

Despite increased intracranial pressure, normal BP is maintained in most elderly patients with nontumoral aqueductal stenosis22 and in animals with hydrocephalic brains.23,24 Jugular venous pressure remains constant, regardless of changes in intraventricular or sagittal sinus venous pressure altered by removal or resection of cerebrospinal fluid in hydrocephalic infants and children.20 Therefore, when BP was reduced in our NaCl-fed rats as a result of an aqueduct block, the BP measurement is likely to represent a fundamental change and is not merely the result of any change in the intraventricular pressure of the brains.

Our working hypothesis (Figure 2) caused us to carry out Experiment 2, and the results seem compatible with this working hypothesis. However, the
results described here by no means provide convincing proof that the hypothesis is valid. Our chief finding is that a block of the aqueduct greatly attenuates hypertension and mortality rate in NaCl-fed DS rats. This experiment was done to test the hypothesis that a high NaCl intake in a susceptible rat could cause the walls of the slitlike 3V to touch and thereby release a neurogenic or neurohumoral NaCl signal that results in hypertension. We suspected the 3V because so many control systems are located in this particular circumventricular area.$^8$,$^9$,$^{21}$ However, we also caused hydrocephalus of the lateral ventricles, and it is still quite possible that the NaCl signal is perceived in structures that reside in the wall of the lateral brain ventricle. Moreover, we have not even demonstrated that an excess of ECF exists in tissues surrounding the 3V during high NaCl feeding. It is also possible that the aqueduct block is preventing a neurohumoral substance, which is secreted in the 3V, from reaching some critical receptor site in tissues surrounding the 4V and thereby activating a hypertension-generating pathway. The hydrocephalus itself could be reducing BP by actions that have nothing to do with contact of the opposite walls of the 3V. This article mainly provides evidence, first, that the NaCl signal is likely not a small increase in the concentration of NaCl in the ECF and, second, that hydrocephalus produced by a block of the aqueduct causes a striking decrease in BP and mortality rate in NaCl-fed DS rats. This is a very unexpected finding and could provide important clues concerning the way that the NaCl signal is perceived. Furthermore, if the NaCl signal is generated by the walls of the 3V or lateral brain ventricles, the pathway of the signal is very much in doubt. However, there are many central nervous system structures in the area, including the organum vasculosum of the lamina terminalis, the subfornical organ, the paraventricular nuclei, and the suprachiasmatic nuclei that can have a strong influence on the level of BP.

Ritter and Dinh$^{33}$ found that the ventricles enlarged and brain structures diminished during the development of hypertension in spontaneously hypertensive rats. A likely explanation of their study could be that hypertension caused brain lesions, and the ventricles enlarged as the neuron volume decreased. In their study, the ventricles enlarged in step with the increasing BP. In our study, enlarging brain ventricles resulted in a decrease in BP. Further inquiry would be useful to find out whether there exists some common mechanism between their study and ours.

When we produced the aqueduct block, the cannula tip pierced normal brain tissue on the way to the aqueduct. This damage of tissue might have contributed to the lowering of BP in the NaCl-fed DS rats. However, when the thermal lesions were made, the cannula tip pierced those same brain structures, and the BP subsequently increased slightly rather than markedly decreasing, as seen after the aqueduct block.

In Experiment 1, the DS rats drinking the hypertonic solution ingested three times more fluid than those drinking the hypertonic solution. However, it is unlikely that the large volume of water taken in by these rats is responsible for their hypertension. Because they were bred to be highly NaCl sensitive, it is most probable that the high NaCl aspect of their total intake is the initial cause of their hypertension.

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**References**


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